

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-457

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-457

Drug Name: Volare HFA (Albuterol Sulfate) Inhalation Aerosol

Indication(s): Treatment or prevention of bronchospasm with reversible obstructive airway disease

Applicant: Ivax Research, Inc.

Documents Reviewed: Volume 1.1 module 1, Volume 1.3 module 2, Volume 1.10 and 1.17 module 5
Dated January 30, 2003.
Volumes dated August 5, 2003 and August 15, 2003.
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Review Priority: Standard

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Content and Format

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1. Executive Summary

1.1 Conclusions and Recommendations

The sponsor submitted this application of Volare (Albuterol Sulfate) HFA MDI as a 505(b)(2) application for the treatment or prevention of bronchospasm with reversible obstructive airway disease. The sponsor only studied their albuterol HFA MDI in asthmatics.

The sponsor demonstrated efficacy compared to placebo for their Albuterol HFA given by MDI for the primary analysis of endpoint AUC FEV₁ above baseline in Study BNP-301- 4-167. Efficacy for this endpoint was also seen in the intent-to-treat analysis in the single dose crossover study BNP-301- 4-105. Efficacy compared to placebo was also seen for peak FEV₁ above baseline in these two studies. Comparable efficacy to Proventil HFA for these endpoints was seen in these two studies. From a statistical viewpoint, this submission is approvable. The labeling indication is a review issue.

1.2 Brief Overview of Clinical Studies

This review will focus on the single dose crossover study BNP 301- 4-105 and the 43 day parallel group study BNP-301-4-167.

Study BNP-301- 4-105 was a multicenter, evaluator-blind, placebo-controlled, seven-period, single-dose, crossover study comparing Placebo HFA-MDI (3 actuations), Albuterol-HFA-MDI 90 mcg (1 actuation), Albuterol-HFA-MDI 180 mcg (2 actuations), Albuterol-HFA-MDI 270 mcg (3 actuations), Proventil HFA 90mcg (1 actuation), Proventil 180 mcg (2 actuations), and Proventil HFA 270 mcg (3 actuations) in moderate-to-moderately severe asthmatics. There was a 2-14 day washout between treatments. During each treatment period, FEV₁ determinations were made 30 minutes and immediately before dosing and 0.083, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, and 6 hours following dosing.

The sponsor analyzed AUC FEV₁ above baseline and Maximum FEV₁ above baseline by a mixed model with sequence, period and treatments as fixed effects and subjects within sequence as a random effect.

This reviewer could not verify the sponsor's results for Maximum FEV₁ above baseline from the data files provided. On July 25, 2003 a facsimile was sent to the sponsor inquiring to the reason that analyses from the data file did not agree with the results in the study report. In the sponsor's August 5, 2003 submission, the sponsor stated that for the MITT analyses, the time zero values could mistakenly be used to calculate maximum FEV₁ for the MITT Population but not for the per-protocol analyses, which is not discussed in this review. [The MITT population was all patients who received at least one treatment.] The sponsor provided new analyses for Maximum FEV₁ for the MITT population in the August 5, 2003 submission. The sponsor was sent a facsimile on August 15, 2003, to provide a new dataset for Study BNP 301-4-105 correcting the Maximum FEV₁ values. The corrected dataset was submitted on August 15, 2003 to the Electronic Document Room.

Study BNP- 301-4-167 was a multi-center, randomized, evaluator-blind (double-blind/double-dummy vs placebo for the Ivax products), placebo-controlled, parallel group study comparing Placebo, Albuterol-HFA-MDI 180 mcg, Albuterol-HFA-BOI 180mcg, and Proventil HFA 180 mcg. [The Albuterol-HFA-BOI product is another IVAX product] Patients received treatments four times a day for 42 days and returned for a clinic evaluation at Day 43. At Days 1, 22, and 43, FEV₁ determinations were made 0.5 hours and immediately before dosing and 0.083, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, and 6 hours following dosing.

The sponsor analyzed AUC FEV₁ above baseline by a one-way analysis of variance with treatments as the fixed factor. The primary efficacy analysis was AUC FEV₁ above baseline at Endpoint.

This reviewer noticed that different results for AUC FEV₁ above baseline could be derived from data contained in the Study folder from that contained in the ISE folder. The Sponsor explained in their August

5, 2003 submission that the AUC FEV₁ in the study report was based on the targeted assessment times whereas the AUC FEV₁ in the ISE folder were based on the observed assessment times. This review will give the results using the observed assessment times. [The results of the two analyses were very similar because 331/345 (96%) of the calculated AUC FEV₁ values were identical.] [Many sponsors use linear interpolation to calculate values that will be used in the AUC calculation. These interpolated values are also used in graphs of the serial FEV₁ means.]

1.3 Statistical Issues and Findings

Fifty-eight patients entered the Study BNP-301-4-105 of whom 47 completed the study. Table 1 below provides the p-values comparing active treatments with placebo for AUC FEV₁ above baseline. All active treatments were significantly different from placebo. Table 1 corresponds to sponsor's table 14B.2.1.1 (Volume 1.10 Module 5). The largest difference between the sponsor's Albuterol-HFA-MDI and Proventil's Least Squares Means was for the 270 mcg dose where the difference was -0.15 with S.E. of 0.16 and a P-value of 0.3470.

Table 1 Comparison Between Each Active Group and Placebo of Baseline Adjusted Area Under The FEV₁ Curve (AUC 0-6 HR*L) –MITT Population (N=58)

Treatment Group	Raw Mean (S.E.)	Least Squares Mean (S.E.)	Difference (S.E.) (Active – Placebo)	P-Value Versus Placebo
Placebo	0.42 (0.15)	0.48 (0.18)		
Albuterol HFA MDI 90 mcg	1.39 (0.19)	1.38 (0.18)	0.90 (0.16)	<0.0001
Proventil HFA 90 mcg	1.28 (0.19)	1.29 (0.18)	0.81 (0.16)	<0.0001
Albuterol HFA MDI 180 mcg	1.56 (0.18)	1.55 (0.18)	1.08 (0.16)	<0.0001
Proventil HFA 180 mcg	1.55 (0.18)	1.53 (0.18)	1.05 (0.16)	<0.0001
Albuterol HFA MDI 270 mcg	1.66 (0.21)	1.66 (0.18)	1.18 (0.16)	<0.0001
Proventil HFA 270 mcg	1.80 (0.19)	1.82 (0.18)	1.34 (0.16)	<0.0001

Baseline adjusted area under the curve. Baseline adjustment obtained by subtracting the average of the two pre-dose FEV₁ determinations from each post-dose FEV₁ determination.

P-values derived from a mixed effects model with fixed effects of sequence, period and treatment group, and random effect of subject within sequence.

Table 2 provides, for Study BNP-301-4-105, the p-values for comparing active treatments with placebo for Maximum FEV₁ above baseline. Table 2 corresponds to Table 14B.2.2.1 of the sponsor's August 5, 2003 submission. The largest difference between the sponsor's Albuterol-HFA-MDI and Proventil's Least Squares Means was for the 270 mcg dose where the difference was -0.01 with S.E. of 0.03 and a P-value of 0.7551.

Table 2 Comparison Between Each Active Group and Placebo of Baseline Adjusted Maximum FEV₁ (L) – MITT Population (N=58)

Treatment Group	Raw Mean (S.E.)	Least Squares Mean (S.E.)	Difference (S.E.) (Active – Placebo)	P-Value Versus Placebo
Placebo	0.22 (0.04)	0.23 (0.03)		
Albuterol HFA MDI 90 mcg	0.44 (0.03)	0.43 (0.03)	0.20 (0.03)	<0.0001
Proventil HFA 90 mcg	0.43 (0.04)	0.43 (0.03)	0.20 (0.03)	<0.0001
Albuterol HFA MDI 180 mcg	0.47 (0.03)	0.47 (0.03)	0.24 (0.03)	<0.0001
Proventil HFA 180 mcg	0.47 (0.04)	0.46 (0.03)	0.23 (0.03)	<0.0001
Albuterol HFA MDI 270 mcg	0.50 (0.04)	0.50 (0.03)	0.27 (0.03)	<0.0001
Proventil HFA 270 mcg	0.51 (0.04)	0.51 (0.03)	0.28 (0.03)	<0.0001

Baseline adjusted Maximum FEV₁. Baseline adjustment obtained by subtracting the average of the two pre-dose FEV₁ determinations from each post-dose FEV₁ determination.

P-values derived from a mixed effects model with fixed effects of sequence, period and treatment group, and random effect of subject within sequence.

There were 345 patients (58 Albuterol-HFA-MDI, 173 Albuterol-HFA-BOI, 56 Proventil HFA, 58 Placebo) randomized into Study BNP-301- 4-167 of whom 290 completed the study (52 Albuterol-HFA-MDI, 141 Albuterol-HFA-BOI, 50 Proventil HFA, 47 Placebo). The treatment groups were comparable in demographic variables and baseline pulmonary function.

Table 3, below, (from Sponsor's Table 11-5, Module 5, Volume 1.17) provides the results of the analyses of AUC₀₋₆ FEV₁ At Endpoint calculating AUC using scheduled serial assessment times. All three active treatments were significantly different from placebo with no significant difference among active treatments. Table 4 (from Sponsor's Tables 2.1 and 2.2 Module 2, Volume 1.3, Appendix 2.7.3.6) below provides a similar analysis using the calculation method found in the ISE, using actual assessment times. There was very little difference between the two methods used to calculate AUC's.

Table 3 BNP-301-4-167, AUC₀₋₆ (L•Hr) of baseline-adjusted FEV₁, At Endpoint, MITT¹ Study Report Definition

Treatment	N	Mean (SD)	LS Mean (STE)	Treatment Comparison	LS Mean Diff (STE) ²	p-value ²
Overall (All study days)						
A) Albuterol HFA-MDI	58	1.28 (1.68)	1.28 (0.17)	A-D	1.04 (0.24)	0.0000
B) Albuterol HFA-BOI	173	1.28 (1.68)	1.28 (0.17)	B-D	1.04 (0.24)	0.0000
C) Proventil HFA	56	1.20 (1.25)	1.20 (0.18)	C-D	0.97 (0.25)	0.0001
D) Placebo	58	0.23 (0.92)	0.23 (0.17)	A-C	0.07 (0.25)	0.7732
				B-C	0.07 (0.25)	0.7732
				A-B	0.07 (0.25)	0.7732
				Treatment		0.0000

Table 4 BNP-301-4-167, AUC₀₋₆ (L•Hr) of baseline-adjusted FEV₁, At Endpoint, MITT¹ ISE Definition

Treatment	N	Mean (SE)	LS Mean (STE)	Treatment Comparison	LS Mean Diff (STE) ²	p-value ²
Overall (All study days)						
A) Albuterol HFA-MDI	58	1.28 (0.22)	1.28 (0.17)	A-D	1.04 (0.24)	<0.0001
B) Albuterol HFA-BOI	173	1.28 (0.22)	1.28 (0.17)	B-D	1.04 (0.24)	<0.0001
C) Proventil HFA	56	1.20 (0.17)	1.20 (0.18)	C-D	0.97 (0.25)	0.0001
D) Placebo	58	0.24 (0.12)	0.24 (0.17)	A-C	0.08 (0.25)	0.7594
				B-C	0.08 (0.25)	0.7594
				A-B	0.08 (0.25)	0.7594
				Treatment		0.0000

The sponsor did not provide an endpoint analysis of maximum FEV₁ above baseline in this study. The sponsor analyzed maximum FEV₁ above baseline by a mixed effect ANOVA with treatment, study day, and treatment-by-study day interaction as fixed effects, and patients as a random effect. Because the study day-by-treatment interaction is not significant (p=0.5735) the comparison of treatments averaged over all treatment days will be presented in Table 5 (from Sponsor's Table 14.2.7.1 , module 5, volume 1.18) . All active treatments are significantly different from placebo with little differences between active treatments.

Table 5 BNP-301-4-167, Maximum FEV₁ of baseline-adjusted FEV₁, Overall Study Days, MITT Population

Treatment	N	Mean (SD)	LS Mean (STE)	Treatment Comparison	LS Mean Diff (STE) ²	p-value ²
Overall (All study days)						
A) Albuterol HFA-MDI	58	0.46 (0.247)	0.46 (0.028)	A-D	0.27 (0.040)	0.0000
B) Albuterol HFA-BOI	173	—	—	B-D	—	—
C) Proventil HFA	56	0.43 (0.200)	0.43 (0.028)	C-D	0.24 (0.040)	0.0000
D) Placebo	58	0.19 (0.126)	0.19 (0.028)	A-C	0.03 (0.040)	0.3934
				B-C	—	—
				A-B	—	—
				Treatment		0.0000

1.4 Statistical Conclusions

The sponsor demonstrated efficacy compared to placebo for their Albuterol HFA given by MDI for the primary analysis of endpoint AUC FEV₁ above baseline in Study BNP-301- 4-167. Efficacy for this endpoint was also seen in the intent-to-treat analysis in the single dose crossover study BNP-301- 4-105. Efficacy compared to placebo was also seen for peak FEV₁ above baseline in these two studies. Comparable efficacy to Proventil HFA for these endpoints was seen in these two studies.

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